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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/889,355	07/08/97	ENGLER H	16930-000811

HM12/0709

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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	9

DATE MAILED: 07/09/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/889,355	Applicant(s) Engler H. et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Apr 2, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-61* is/are pending in the application.

Of the above, claim(s) *56-61* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-55 and newly added claims 56-61 are pending in the instant application.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 56-61 are withdrawn from consideration as being directed to a non-elected invention that is a method of delivering a diagnostic agent to a cell. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-55 under consideration in the instant application.

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent application); the disclosure of the invention in the parent application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

The parent application 08/584,077, filed January 8, 1996, U.S. Patent 5,789,244, upon which priority is claimed fails disclose the invention and does not provide adequate support under 35 U.S.C. 112 for claims 1-61 of the instant application. The specification of the parent application 08/584,077 does not disclose the invention of claims 1-60 or enable claims 1-9 and 11-60 because the compounds of Formulas I-V claimed in the instant invention are not disclosed in application 08/584,077, because compounds claimed in the instant invention are the enhancing

agent of the instant application and are essential to the invention and because Patent 5,789,244 does not contemplate enhancing delivery of DNA of proteins using the compounds claimed in the instant invention. Therefore, the effective filing date of the instant application is July 8, 1997.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue BigCHAP is not within the scope of the formula recited in the specification. Applicants argument is persuasive as the formulas describe impurities found within BigCHAP and not BigCHAP. However, it is noted that the claims encompass delivering a therapeutic molecule using the impurity in Formula I with BigCHAP because of the open "comprising" language used in the claims.

Applicants argue the various impurities found in some commercial preparations of BigCHAP responsible for enhancing delivery of therapeutic agents. Applicants argument is not persuasive because it is unclear which impurities enhance delivery of therapeutic agents. Example

11 describes using impurities I, II and III isolated from BC BigCHAP. The specification states only two of the impurities demonstrate improved gene transfer and expression (page 29, line 6). Specifically, it appears as though impurity I does not increase gene expression (page 30, line 14). However, it is unclear what impurities I, II and III are because the formula for the impurities is not provided. Therefore, it is unclear which formulas claimed enhance delivery of DNA. In addition, the synthesis of specific compounds as in example 12 does not provide one of skill with the ability to use such a compound to enhance delivery of a compound since some impurities do not improve delivery. Overall, it is unclear which formulas claimed can be used to improve delivery of therapeutic agents.

Applicants argue the specification demonstrates enhanced delivery of a therapeutic genes using the claimed invention because in example 6, the specification states "enhanced expression using an ethanol of BigCHAP formulation... are shown in Figure 9." Applicants argument is not persuasive because the specification states "enhanced expression using an ethanol **or** BigCHAP formulation are shown in Figure 9" and because Figure 9 appears to demonstrate expression using ethanol alone as an enhancing agent and not BigCHAP. It is noted that example 6 uses BigCHAP containing the impurities to obtain enhanced delivery of the gene which is within the scope of the claims. Applicants argue the specification contains several examples demonstrating b-gal is enhanced when administered using a formulation containing the compounds claimed. Applicants argument is persuasive.

Applicants argue the references regarding the unpredictability in the art of gene therapy do

not reflect the state of the art when taken alone. Applicants arguments are not persuasive because the references of record clearly state that it is unpredictable what vector, promoter, mode of delivery and dosage of a gene are required to obtain a therapeutic result (Eck and Wilson, Verma et al., Ross et al. and Marshall of record). While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels; i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Applicants argue some of the references cited indicate that gene therapy could be improved by methods of enhancing delivery of DNA (page 7). Applicants argument is persuasive; however, it is not clear which impurities in the instant application can be used to enhance delivery of DNA.

Applicants argue that the state of the art is more accurately depicted by the gene therapy clinical trials that are underway. Applicants argument is not persuasive because of the lack of correlation between expression of a gene product and therapeutic value in the field of gene therapy as taught by Verma et al. of record by stating "Although more than 200 clinical [gene therapy] trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (page 239, column 1, line 16). Thus, it is unpredictable whether gene therapy in clinical trials will result in a therapeutic effect. Applicants argue that the clinical trials require a demonstration of pharmaceutical efficacy that is greater than 35 USC 112. Applicants argument is not persuasive because while clinical trials may

provide a possibility of success, based on what was known in the art at the time of filing, one of skill could not predict whether a therapeutic effect could be obtained with a reasonable expectation of success.

Applicant argues the rejection of claims 7, 16 and 29 is unclear because claim 7 is directed to a method of administering a protein to a cell, claim 16 is directed to a pharmaceutic composition and claim 29 is the only claim directed toward treating bladder cancer. Applicants argument is not persuasive because the claims are all directed toward administering a therapeutic or pharmaceutical protein which has not been adequately disclosed in the specification such that one of skill would have a reasonable expectation of success in obtaining a therapeutic effect. Applicants argue the phrase "without causing any phenotypic change to the host" is unclear. The intent of the examiner is to indicate that claim 29 is directed toward a method of gene therapy, but the claim does not indicate what applicants consider to be the therapeutic outcome and the specification does not provide adequate guidance as to whether applicants intend to reduce tumor burden, prevent metastases, eliminate tumors completely or extend the life span of a person with bladder cancer.

Claim Rejections - 35 USC § 102

3. Claims 1, 7, 12, 16, 23, 29, 41-42, 45, 54 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) is maintained because BigCHAP inherently contains the impurity of Formula I.

Aungst et al. teach the delivery of insulin with various surfactants including BigCHAP to

rats (page 230, Figure 1). Applicants argue Formula I is not BigCHAP, but rather an impurity found in BigCHAP; therefore, applicants argue Aungst et al. do not anticipate the claims. Applicants argument is not persuasive because the BigCHAP taught by Aungst et al. inherently contains the impurity of Formula I. Thus, Aungst et al. delivers a therapeutic molecule formulated in a buffer comprising a compound of Formula I as claimed. Claims 41-42 and 45-46 are drawn toward compounds of Formula I which are anticipated by the compound BigCHAP as disclosed in Aungst et al. because BigCHAP inherently contains Formula I and the variations of Formula I claimed. Claims 54 and 55 drawn to the impurity of Formula II are anticipated by the BigCHAP as disclosed in Aungst et al. because BigCHAP inherently contains Formula II and the variation claimed in claim 55.

Claim Rejections - 35 USC § 103

4. Claims 1-6, 8, 12-15, 17, 23-26, 30, 39-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Aungst et al. do not teach the method of administering a gene to a cell comprising the gene formulated in a buffer comprising a compound of Formula I as described in the claims. However, at the time of filing Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). The formulations in claims 42-53 are impurities also

found in BigCHAP as taught by Aungst et al. and are obvious variations of the impurity of Formula I (claim 41) found in BigCHAP. Formula II (claim 54) is an impurity found in BigCHAP as taught by Aungst et al. and the variation in claim 55 is an obvious variant of Formula II. Applicants argue Formula I is not BigCHAP, but rather an impurity found in BigCHAP; therefore, applicants argue Aungst et al. and Carson et al. do not make the claims obvious. Applicants argument is not persuasive because the BigCHAP taught by Aungst et al. contains the impurity of Formula I. Thus, the formulation of a therapeutic agent in BigCHAP as taught by Aungst et al. obviously comprises Formula I as claimed.

5. Claims 1, 8-10, 12, 17-19, 23 and 30-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) as applied to claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 above, and further in view of Wills et al. (1994, Human gene therapy, Vol. 5, pages 1079-1088).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). Wills et al. disclose the adenovirus encoding p53 for delivery to tumor cells. Applicants argue Formula I is not BigCHAP, but rather an impurity found in BigCHAP; therefore, applicants argue Aungst et al. does not make the claims obvious. Applicants argument is not persuasive because the BigCHAP taught by Aungst et al. contains the impurity of Formula

I. Thus, the formulation of a therapeutic agent in BigCHAP as taught by Aungst et al. obviously comprises Formula I as claimed.

6. Claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) as applied to claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 above, and further in view of Takahashi et al. (1991, Proc. Natl. Acad. Sci. USA, Vol. 88, pages 5257-5261).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). Takahashi et al. disclose the delivery of a gene encoding full length RB protein into bladder carcinoma (page 5258, column 2, line 8 and line 16). Applicants argue Formula I is not BigCHAP, but rather an impurity found in BigCHAP; therefore, applicants argue Aungst et al., Carson et al. and Takahashi et al. do not make the claims obvious. Applicants argument is not persuasive because the BigCHAP taught by Aungst et al. contains the impurity of Formula I. Thus, the formulation of a therapeutic agent in BigCHAP as taught by Aungst et al. obviously comprises Formula I as claimed.

Claims 21, 22, 35 and 36 are free of the art.

This action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson
July 1, 1999

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630